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EDITORIAL COMMENT

Low High-Density Lipoprotein Cholesterol and Chronic Disease Risk

Marker or Causal?*

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Numerous epidemiological studies have demonstrated a strong inverse relationship between high-density lipoprotein cholesterol (HDL-C) and the risk of cardiovascular events (1). In this issue of the *Journal*, a meta-analysis of lipid-modifying drug trials has extended the harmful association of low HDL-C to increased risk of cancer (2). Does low HDL-C cause cancer (or even cardiovascular disease for that matter)? Evidence of causality would suggest that interventions to increase HDL-C could decrease the risk of the 2 most important causes of morbidity and mortality in the U.S. (3). Short of randomized clinical trial data as proof of causality, epidemiologists have developed several criteria for determining causality from observational data. Evidence for a causal relationship between HDL-C and cancer or cardiovascular disease is reviewed in the following text and summarized in Table 1.

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Temporality

Did the low HDL-C levels predate the disease or did the disease cause low HDL-C levels (also known as reverse causality)? For example, evidence of reverse causality has been found for low total cholesterol levels associated with an increased cancer risk. A recent analysis of the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer) Prevention Cohort of 29,093 male Finnish smokers followed for 18 years found that the inverse association between total cholesterol and cancer entirely disappeared when cancer cases diagnosed during the first 9 years of follow-up were excluded (4). Another large cohort study in men found that total cholesterol levels started to decrease approximately 5 years before cancer diagnosis (5). Therefore, reverse causality explains the relationship to low low-density lipoprotein (LDL) cholesterol, which largely constitutes total cholesterol, previously described by this group in the *Journal* (6). In contrast, reverse causality does not appear to explain the relationship between low HDL-C and cancer. In the ATBC study, the relationship between low HDL-C and increased cancer risk (highest to lowest quintile, relative risk: 0.89; 95% confidence interval: 0.83 to 0.97, p for trend = 0.01) persisted after excluding cancer cases diagnosed within 12 years of study entry, and there is no evidence of reverse causality for HDL-C and cardiovascular disease. In the Framingham study, low HDL-C at baseline predicts increased cardiovascular risk 30 years later (7).

Dose Response

In their meta-analysis, Jafri et al. (2) report a 36% lower cancer rate for each 10-mg/dl increase in HDL-C. The ATBC investigators also found evidence of a dose-response relationship, although a less robust one, of an approximately 5% lower cancer rate per 10-mg/dl increase in HDL-C up to a level of 55 mg/dl (4). For cardiovascular disease, each 1-mg/dl higher increment in HDL-C is associated with a 2% to 3% decrement in cardiovascular risk (1).

Biological Plausibility

The protective cardiovascular effects of high-density lipoprotein (HDL) are largely attributed to reverse cholesterol transport of cholesterol from lipid-laden macrophages in peripheral tissues to the liver for catabolism and excretion into bile (8). HDL may have other antiatherosclerotic, as well as anticancer, effects attributable to its antioxidant and anti-inflammatory properties. HDL can prevent LDL oxidation, thereby inhibiting the inflammatory response induced by LDL-derived oxidized lipids (9). Antioxidant enzymes paraoxinase-1 and platelet-activating factor acetylhydrolase are associated with HDL-C. HDL is known to inhibit monocyte binding, up-regulate nitric oxide release, reduce monocyte apoptosis induced by cholesterol loading, preserve monocyte viability by prevention of post-apototic necrosis, reduce macrophage excretion of inflammatory cytokines, and inhibit monocyte attraction (10). Additional mechanisms for protective cancer effects of HDL-C may be due to influences on the cell cycle via a mitogen-activated protein kinase-dependent pathway or regulation of apoptosis (4).

Alternate Explanations

Is low HDL-C simply a marker for smoking, obesity, inflammation, or hyperinsulinemia, all of which are implicated in the pathogenesis of both atherosclerosis and of carcinogenesis? Notably, all participants in the ATBC trial were smokers (which also lowers HDL-C) (4). Oxidative enzymes at sites of inflammation can modify apolipoprotein

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Table 1 Epidemiological Criteria for Causality for HDL-C and Cancer or Cardiovascular Disease

Criteria	Cancer	Cardiovascular Disease
Exposure predates disease	Yes	Yes
Dose response	Yes	Yes
Biological plausibility	Yes	Yes
Consistency of data	No	Yes
Alternate explanations excluded	No	No
Randomized trials	No	No

HDL-C = high-density lipoprotein cholesterol.

(apo) A-I within HDL into a dysfunctional form, impairing reverse cholesterol transport and giving HDL proinflammatory and proatherogenic properties. Inflammation has been shown to lower HDL-C acutely and long term (11) and appears to increase the risk of lung cancer (12). Adiposity lowers HDL-C, increases inflammation and insulin resistance, and increases the risk of several malignancies, including prostate and breast cancer (13,14). Insulin is a growth factor, and high insulin levels have been associated with an increased risk of prostate cancer. Diabetes is associated not just with lower HDL-C levels but also dysfunctional HDL associated with glycation (9). Those with metabolic syndrome or abdominal adiposity also have increased levels of inflammatory HDL, which may become less inflammatory with weight loss (9). Lifestyle interventions to increase HDL-C may also decrease the risk of cancer. Aerobic exercise, tobacco cessation, weight loss, and dietary factors (omega-3, omega-6 polyunsaturated fatty acids, monosaturated fatty acids), taken together, can increase HDL-C 2% to 30%, and a trial of the Mediterranean diet has reported decreased cancer risk (14,15).

Consistency of Data

Data are not consistent for the association between HDL-C and cancer. Prospective studies that included women found low HDL-C levels to be associated with an increased risk of breast and lung cancer (16). However, the Framingham study revealed no relationship between HDL-C and cancer risk or noncoronary heart disease mortality (17). On the other hand, for cardiovascular disease, HDL-C has consistently been shown to have an independent inverse relationship with cardiovascular disease (18).

Proof by Experiment

The gold standard for demonstrating causality is the randomized, controlled clinical trial in which the only variable that changes is the exposure. The meta-analysis by Jafri et al. (2) did not find a relationship between on-treatment HDL-C increases and cancer or any evidence of heterogeneity between the various classes of drugs evaluated. In neither the Jafri et al. (2) paper nor this group's previous statin meta-analysis (6) was there evidence of a relationship between statins, which modestly increase HDL-C by 3% to 8%, and cancer.

In addition to lifestyle and statins, several agents increase HDL-C through a variety of mechanisms. The most effective agent currently available for increasing HDL-C is niacin, which increases HDL-C by 20% to 30% (15). In the Coronary Drug Project, men treated with niacin during the 5-year trial had a significantly lower mortality rate than the placebo group after 15 years of follow-up (19). The mean 1.5-year additional survival in the niacin group was largely attributable to fewer cardiovascular deaths; cancer deaths were similar (4.0% vs. 4.4%, $p = 0.2$). Fibrates can increase HDL-C by 10% to 20% (15). Although more malignancies were initially reported with clofibrate and gemfibrozil in 5-year primary prevention trials, with long-term follow-up, there were no significant increases in cancer incidence or mortality with gemfibrozil, even with follow-up as long as 18 years in the Helsinki Heart Study (20–22). Cancer incidence was similar for both the fenofibrate and placebo groups (8%) in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study (23).

Currently there is insufficient evidence to conclude that pharmacologically increasing HDL-C per se reduces cardiovascular events. A meta-analysis of randomized trials of statins, niacin, and fibrates found that after adjusting for LDL cholesterol changes, pharmacologically increasing the HDL-C level did not reduce the risk of coronary heart disease events or all-cause death, but did not report on cancer rates (24). Although the recent Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies trial found promising evidence that niacin may induce atherosclerotic regression as measured by carotid intimal medial thickness, serious methodological problems, the short duration of the trial, and the lack of reporting end points by HDL-C response limit conclusions regarding the effect of HDL-C increasing per se or of niacin combined with statin therapy on cardiovascular events (25,26).

Cholesteryl ester transfer protein (CETP) inhibitors and several other HDL-C–increasing agents are in development. CETP gene deficiency mutations that increase HDL-C levels have been associated with exceptional longevity. This may be due to lower cardiovascular disease mortality and a healthy survivor effect (absence of 6 major age-related diseases, including cancer, and high cognitive and physical functioning) rather than a decrease in noncardiovascular disease mortality (27). However, a large trial of the CETP inhibitor torcetrapib, which increased HDL-C by 50%, was stopped early due to excess total mortality in the torcetrapib group, although similar rates of cancer were reported. Development of dalcetrapib and anacetrapib, which do not appear to have the off-target blood pressure effects of torcetrapib, is ongoing (28). Apo A-I Milano has not moved forward in development. However, apo A-I mimetics appear promising. The apo A-I mimetic 4F binds oxidized lipids 5 million-fold better than native apo A-I, and the removal of oxidized lipids has been associated with resolution of inflammatory changes (9).

Several ongoing morbidity/mortality trials are evaluating niacin, fenofibrate, and CETP inhibitors used in combination with statins. Although the approximately 3- to 5-year duration of these trials should be adequate for evaluating the effects of these agents on cardiovascular disease, the trials may not be of sufficient duration to determine anticancer efficacy.

Conclusions

The inverse relationship between HDL-C levels and cancer or cardiovascular disease meets many criteria supporting a causal relationship (Table 1). However, the most important criteria for causality have not yet been met (lack of alternative explanations and proof by experiment). Low HDL-C levels may simply be a reflection of chronic conditions that increase inflammation and insulin resistance, which may directly influence atherosclerosis and carcinogenesis. Data from ongoing trials are needed before drawing any firm conclusions regarding the role of niacin or any other HDL-C–increasing drugs in either cardiovascular disease or cancer prevention. At this time, the evidence best supports low HDL-C as a marker for an overall increased risk of chronic disease. Clearly, individuals with low HDL-C may experience particular benefit from lifestyle recommendations to quit smoking, improve diet, engage in regular physical activity, and control weight. Regardless of the effects on HDL-C, healthy lifestyle habits have a significant impact on the prevention of most of the chronic diseases associated with aging.

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